IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 94247; 58898/130

In re patent application of

David J. BOVA — **Group Art Unit: 1502**

Serial No.: 08/368,378 — **Examiner: J. Venkat**

Filed: June 14, 1995

For: NICOTINIC ACID COMPOSITIONS FOR TREATING HYPERLIPIDEMIA AND RELATED METHODS THEREOF

DECLARATION UNDER 37 CFR §1.131

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

I, David J. Bova, state and declare that:

1. I am the named inventor of the above-captioned application, which is a continuation-in-part application of U.S. serial No. 08/124,392, filed on September 20, 1993 ("the parent application").

2. In the office action of November 27, 1995, the examiner maintained a rejection of claims 1-9 under 35 USC §102(e), as being anticipated by O'Neill et al., U.S. patent No. 5,268,181 (1993), which was filed on June 29, 1992.

3. As Vice President of Research and Development for KOS Pharmaceuticals, Inc., I prepared a protocol to compare the effect on serum lipids of sustained release nicotinic acid that was administered once-a-day (either in the evening or at night) or twice-a-day during the day. KOS Pharmaceuticals, Inc., the assignee of the above-captioned application, sponsored the study, and I monitored the performance and conduct of the study.

4. The KOS Pharmaceuticals study was conducted with male and female patients having total cholesterol levels greater than

250 mg/dl. The selection criterion for patients was based upon the report of an expert panel of the National Cholesterol Education Program, which was published in *Arch. Intern. Med. 148*: 36 (1988). A copy of the report is attached to this declaration as Exhibit 1. The panel concluded that individuals with blood cholesterol levels ≥ 240 mg/dl should be classified as having "high" cholesterol levels. Therefore, the patients included in the KOS Pharmaceuticals study were considered to have high cholesterol levels, and they were classified as hyperlipidemics. Accordingly, the study was performed to determine a method of treating hyperlipidemia in hyperlipidemics comprising the administration of an effective amount of nicotinic acid once per day in the evening or at night, as stated in claim 1. Relevant sections of the study protocol were attached as Exhibit A in my declaration of August 17, 1995.

5. The results of the KOS Pharmaceuticals study were disclosed in the above-captioned application and in the parent application. The relevant pages of the parent application are attached to this declaration as Exhibit 2. Briefly, we found that the mean blood cholesterol level at baseline and prior to treatment was 282.2 mg/dl. In the group that received nicotinic acid once per day at night, the mean blood cholesterol level decreased 12.3% to 246.9 mg/dl. Analysis of the clinical data revealed that this decrease in blood cholesterol was highly statistically significant. Thus, the administration of a sustained release formulation of nicotinic acid (once per day in the evening or at night) is an effective treatment for hyperlipidemia.

6. The KOS Pharmaceuticals study began in 1990, and the study was conducted in the United States. Data analyses were also performed in the United States. Although the last visit for the last patient took place on March 20, 1991, statistical analyses were performed each time data was entered into the database.

Exhibit 3 presents an analysis of data that had been collected by December 31, 1990, and demonstrates that a statistically significant reduction in total cholesterol was observed by that time. Exhibit 3 also includes copies of medical documents containing the clinical data used in the analysis.

7. As described above, the KOS Pharmaceuticals study verified a method of treating hyperlipidemia in a hyperlipidemic comprising the administration of nicotinic acid once per day in the evening or at night. Moreover, nicotinic acid was administered to patients in combination with a pharmaceutically acceptable carrier. Accordingly, the invention presently described in claim 1 was conceived and reduced to practice in the United States prior to June 29, 1992, the filing date of the O'Neill patent.

8. In the KOS Pharmaceuticals study, patients received nicotinic acid in the form of sustained release tablets containing nicotinic acid, hydroxypropylmethylcellulose, Povidone and stearic acid, as shown in Table I of both the above-captioned application and the parent application. See page 6 of the parent application, which is attached to this declaration as Exhibit 4. Povidone is also known as "polyvinylpyrrolidone," as stated in monograph 7700 in THE MERCK INDEX, 11th Edition (Merck & Co. 1989) at page 1219. See Exhibit 5. We included stearic acid in the formulation of the study as a lubricating agent. See, for example, the parent application at page 5, fourth full paragraph. Accordingly, the use of a formulation for treating hyperlipidemia that comprises nicotinic acid, hydroxypropylmethylcellulose, polyvinylpyrrolidone and the lubricant, stearic acid, antedates the filing date of the O'Neill patent.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false

statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 3/27/96 By: David J. Bova

David J. Bova